The Role of Risk Assessment: A Review Perspective

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Outline

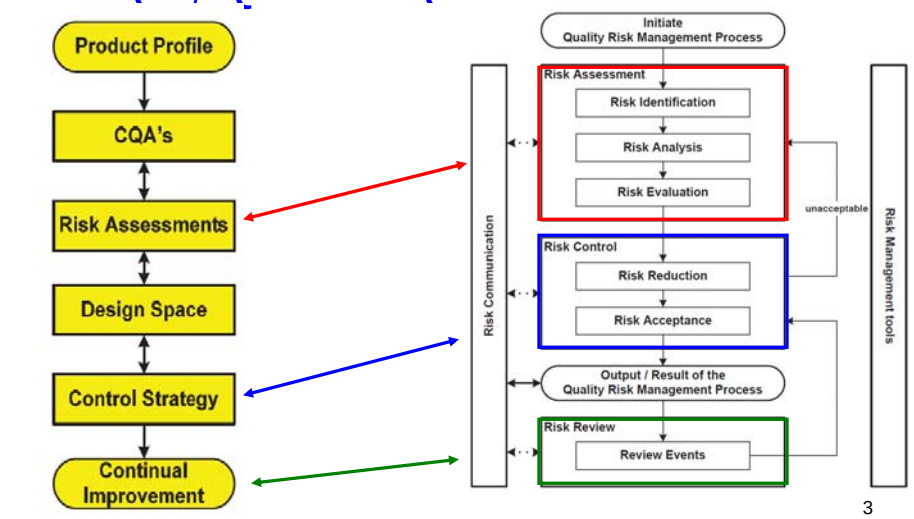
Discussion of role of risk assessment in drug product lifecycle:
- Submissions
- Reviews

Examples of risk assessment in submissions addressing:
- Early Development
- Late Development
- Adequacy of overall control strategy,
- Continual improvement

Examples of risk assessment in review addressing:
- Evaluation of adequacy of control strategy
- Intra-agency communication
- Development of regulatory policies

Conclusion:
- Key components in submission of risk assessments

ICH* Q8, Q9 and Q10:



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*International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Risk Assessment Techniques in Submissions

eCTD section	Sample Techniques
S.2.2 Control of Critical Steps and Intermediates S.2.6 Manufacturing Process Development	Potential Impact Analysis –High/Medium/Low (H/M/L) Criticality Analysis Failure Modes and Effects Analysis (FMEA)
P.2.1 Components	Potential Impact Analysis
P.2.3 Manufacturing Process Development	Process Flow Diagram + Ishikawa Potential Impact/Criticality Analysis Cause and Effect Analysis Summary FMEA –Risk Prioritization Number (RPN) with or without detectability
P.3.2 Manufacturing Process Description	Process Flow Diagram Control Strategy Diagrams Detailed FMEA (RPN with detectability)
P.3.4 Controls of Critical Steps and Intermediates	Criticality Analysis

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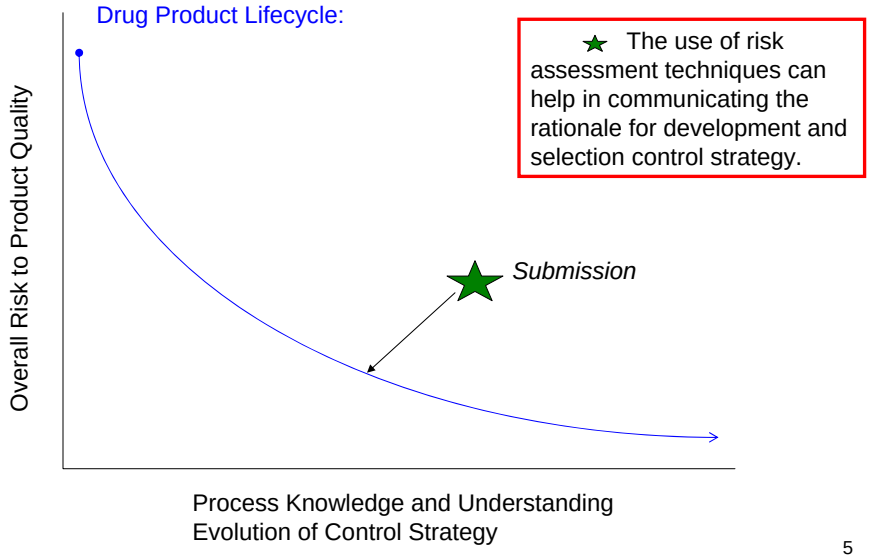

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Examples from Submissions

Risk assessment summaries and results are included in all types of submissions.

- Original New Drug Applications
- Response to Information Requests
- Supplements

Difference in the type of risk assessment used generally depends on

- Stage of development (early vs. late)
- Type of question (general screening vs. specific ranking)

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Example 1: Early Development

Goal: Risk identification and prioritization of development, as to focus on factors with High/Med impact to quality and on unknowns

Tools: Less quantitative approaches that allow risk mapping across a process that may not be completely defined

Examples: evaluation of impact of…

- drug substance attributes on final drug product;
- variance of excipient loading or grade (formulation robustness);
- formulation changes on bioperformance;
- process scale up and starting material specifications on drug substance impurity profile

Outcome:

- capture of prior knowledge within organization,
- formulation and process selections
- justification of areas for study
- overall screening of variables feeding experimental design for late stage

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Early Development: continued

Risk assessment using H/M/L ranking based on severity, as defined

Blending

Variables	Risk	Justification and Experimental Plan
Number of revolutions (Blending Time / Speed)	Medium	
Fill volume	Low	
Lubrication time	Medium	
Input materials	Medium	
Processing and storage condition	Low	

Score	Description	Criteria
10	Extremely severe	Small to moderate change of this attribute or process parameter has a significant impact on a DP CQA
7	Moderately severe	Large change of this attribute or process parameter or a small change in this parameter in combination with other factors has a significant impact on a DP CQA
4	Slightly severe	Large change of this attribute or process parameter in combination with other factors has a significant impact on a DP CQA
1	Not severe	The attribute or process parameter has no impact on DP CQAs

Risk assessment using screening of variable by impact and prior knowledge for further risk assessment

1.5 Jar Milling/Particle Size Reduction

Variable No.	Process Parameter/ Material Attribute	Affected Quality Attributes	Candidate for Rank Scoring	Comment
1.5.1	Bead Type	Particle Size Distribution	No	
1.5.2	Bead Size	Particle Size Distribution	Yes	
1.5.3	Any Other Bead Characteristics	NA	-	
1.5.4	Bead Loading	Particle Size Distribution	Yes	
1.5.5	Active Loading	Particle Size Distribution, Nepafenac Assay	Yes	
1.5.6	Bead Loading to Slurry Volume Ratio	Particle Size Distribution	Yes	
1.5.7	Particle Size Distribution (post-jet mill) for the Active	NA	-	
1.5.8	Sterilization Details for Active/Vehicle (as applicable)	NA	-	
1.5.9	Flow Rate	NA	-	
1.5.10	Milling RPM	Particle Size Distribution, Nepafenac Assay	Yes	
1.5.11	Milling Time	Particle Size Distribution	Yes	
1.5.12	Milling Equipment Geometry	-	No	
1.5.13	Aseptic Milling	Sterility	No	

•Comments sections **convey rationale** and **input into experimental or development plans**
•Can include reference to development documents or data in submission

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Early Development: continued

Drug Substance CQA	Analytical Method	Is the CQA of the Drug Substance Impacted by a Specific Process Parameter or Synthesis Step?				
		Step 1	Step 2	Step 3	Step 4	Step 5
1. Appearance[a]		No	No	No	No	No
2. Identification[a]		No	No	No	No	No
3. Assay[b]		No	No	No	No	No
4. Purity - Organic		**Yes**	No	**Yes**	**Yes**	No
5. Purity - Stereoisomeric		No	No	**Yes**	**Yes**	No
6. Purity - Residual Solvents[a]		No	No	No	**Yes**	No
7. Purity – Inorganic[a]		No	No	**Yes**	No	No
8. Purity - Heavy Metals[a]		No	No	No	No	No
9. Particle Size[a]		No	No	No	No	**Yes**
Conclusion on Criticality of Synthesis Step:		**Critical**	**Non-critical**	**Critical**	**Critical**	**Critical**

CQA	step	step	step	step	step	step
Description	Medium	Medium	Low	Medium	Low	Medium
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low
Absolute configuration	Low	Low	Low	Low	Low	Low
Organic impurities	Medium	Medium	Low	Medium	Medium	Medium
Solvents	Low	Low	Low	Low	Low	Medium
Water	Low	Low	Low	Low	Low	Low
Sulphated ash	Low	Low	Low	Low	Low	High
Polymorphic form	Low	Low	Low	Low	Low	Medium
Particle size	Low	Low	Low	Low	Low	Medium
Metals	Low	Low	Low	Low	Low	Low
Microbiology[a]	Low	Low	Low	Low	Low	Low

[a] Total aerobic microbial count and total combined yeasts and moulds count.
Low — Low risk of step affecting the critical quality attribute.
Medium — Medium risk of step affecting the critical quality attribute.
High — High risk of step affecting the critical quality attribute.

- Criticality analysis based on potential impact of variables on CQA for drug substance;
- YES/NO or H/M/L impact
- Rationale for selection of process steps for further study captured in body of text.

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Example 2: Late Development

Goal: Failure mode identification, evaluation and control for factors that have impact on drug product quality.

Tools: Typically more quantitative approaches to allow decision-making based on risk prioritization numbers. (or their summary).

Examples: Evaluation of…

- process parameter variance impact on drug substance and drug product quality
- analytical method robustness,
- risk of scale up and late process changes,
- analysis of adequacy of controls.

Outcomes:

- Selection of critical process parameters and definition of the control strategy;
- Description of parameter ranges with regards to low vs. high risk operation (e.g. Normal vs. Proven Acceptable ranges vs. knowledge space);
- Contribution of detectability and in process controls to overall risk reduction. Proposals for further monitoring.

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Late Development: Continued

1 2 3 4 5

Product Name									
Process Details									
Date Performed									
Variable Number	Variable	CQA Impacted	Weight (W)	Possible Mechanism of Variable Affecting CQA	Importance (I)	Risk Score (W*I)	Potential CPP	Desired Knowledge Range	Recommendation
1.1.1	[redacted] Viscosity	Particle Size Distribution	10		7	70	Yes		
1.1.3	[redacted] Particle Size Distribution	Particle Size Distribution	10		4	40	No		
1.3.2	Autoclave Cycle Details (Dwell Temperature, Dwell Time, F_0)	Particle Size Distribution	10		7	70	Yes		
1.4.1	Jet Milling Parameters for [redacted] (Pressure, Feed Rate, Number of Passes)	Particle Size Distribution	10		7	70	Yes		
1.5.2	Bead Size	Particle Size Distribution	10		10	100	Yes		

1. CQA weight (1-10);
2. Statement of possible mechanism for effect;
3. Potential impact (1-10) on CQA
4. Inclusion of process design targets or "desired knowledge range"
5. Rationale for how study of variable will be in final experiments.

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Late Development: Continued

Step	Unit operation	Effect of scale/equipment	Risk[2]
Intermediate A	Reaction		Low
	Phase separations and evaporation		Low
Intermediate B	Reaction		Low
	Phase separations		Low
	Evaporation		Low
	Isolation		Low

[2] The risk is defined as the risk of having a negative impact on the drug substance CQA when changing scale or equipment. The levels are 'Low', 'Medium' and 'High'.

- Potential negative impact analysis (H/M/L) on CQA due to scale up
- Rationale for not selecting steps for further scale up study.
- Prior knowledge captured in rationale, even for low risk variables in a given step.

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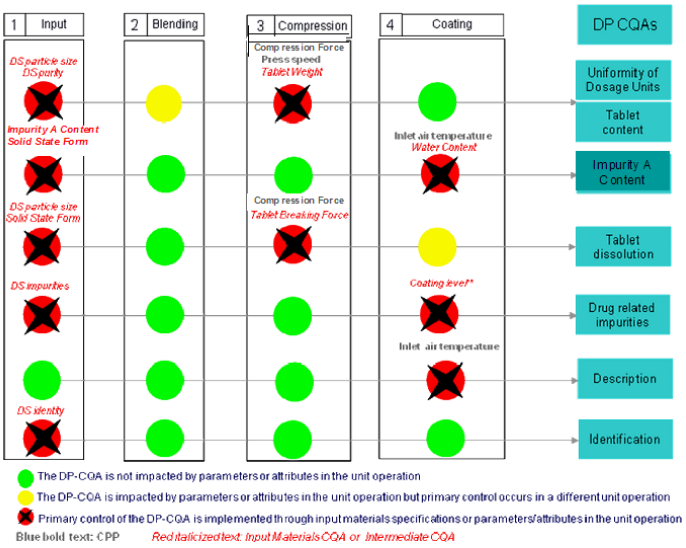
Example 3: Visual Description of Control Strategy



Control strategy diagrams with "level of impact" color coding can convey the level risk (impact) **and** adequacy of controls.

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Example 3: Control Strategy + FMEA

1 2 3 4

Parameter/ Variable Number	Parameter/ Variable	Current Value/Set Point Range	Reference for Current Range	Potential Cause of Failure or Deviation	Probability (P)	CQA Impacted	Impact (I)	Current Detection Mode/ Control Mechanism	Detection (D)	RPN	Mitigation Strategy/ Follow Up Action	Responsibility
1.1.1	[redacted] Viscosity (Incoming)	[redacted]	[redacted]	The acceptance range is [redacted] cps.	1	PSD	7	Through CoA review	7	49		
1.3.2	Autoclave Cycle Details for [redacted] Solution (Dwell Time/ Temperature, F_0)	[redacted]	[redacted]	Incorrect set-up; equipment failure	4	PSD	4	Through review of [redacted] trends	4	64		
1.5.10	Milling RPM	[redacted]	[redacted]	Incorrect set-up; equipment failure	4	PSD	7	Through review of [redacted] trends	7	196	Harm to patient mitigated by particle size distribution testing at prelim stage. Any occurrence should be investigated further to evaluate control strategy.	QA

1. Commercial Operation Ranges
2. Development reference for ranges
3. Failure modes with traditional RPN
4. Risk mitigation as needed.

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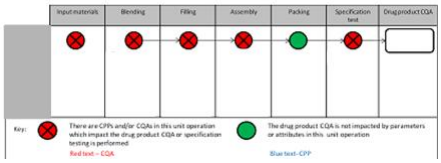
Example 4: Response to information requests:

Risk of holding bulk materials:

Intermediate	Attribute	Risk	Risk Mitigation Strategy
Powder blend	Chemical stability	medium	Test chemical stability
	Blend uniformity	low	No action
	Compressibility	medium	Generate compression profiles
Tablet cores	Chemical stability	medium	Test chemical stability
	Tablet integrity	medium	Test friability and hardness
Coated tablets	Chemical stability	medium	Test chemical stability
	Dissolution	medium	Test dissolution

Controls for a specific CQA:



Abbreviated risk assessment can be used effectively to address information requests or to provide rationales for controls on a specific CQA.

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★ Some key questions from risk-based review perspective:

- Have all the critical quality attributes been identified and ?
- Have the potential risks to quality been identified?
- Is there an adequate level of process knowledge and understanding to address the potential risks and to justify the proposed controls?
- Are the proposed controls sufficient to assure product quality during routine production?

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Risk Assessment in Review

Goal: Risk identification and evaluation of adequacy of controls.

Tools: Typically accommodate less quantitative approach to allow overall mapping and summary of comprehensive control strategy (material, process, analytical) and the link to critical quality attributes.

Outcomes:

- Focus of review on high risk factors to enable targeted questions;
- Evaluation of adequacy of final control strategy;
- Communication of risk intra-agency (e.g. post marketing and/or field investigators during a submission);
- Focus on high risk areas for guidance writing.

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Example: Evaluation of Control Strategy

CQA of finished product	Excipient attributes that could have an impact on CQA	Controls in place
Appearance	Color of coating powder	Monitored by supplier's certificate of analysis
Assay	Particle size of mannitol and micro crystalline cellulose (MCC)	Fineness specification set as given in table 3.2.P.4.1.1-2
Content uniformity	Particle size of mannitol and MCC	Fineness specification set as given in table 3.2.P.4.1.1-2
Degradation (primary factors causing degradation are moisture and oxygen)	Loss on Drying (LOD) of MCC, croscarmellose sodium and hypromellose	Limits in place for acceptable water level that are tighter than ICH guidelines
Dissolution	Particle sizes of croscarmellose and hypromellose; magnesium stearate specific surface area	Fineness specifications for croscarmellose and hypromellose as given in table 3.2.P.4.1.1-2, no specification for magnesium stearate specific surface area
Drug Substance Form	LOD of MCC, croscarmellose sodium and hypromellose	Limits in place for acceptable water level that are tighter than ICH guidelines

Reviewer assessment of adequacy of control strategy for control of drug substance impurities (ICH Q11)

Potential Genotoxic and Other Impurities

Compound	PDE or TTC in DS	In-Process Monitoring	Control Points	Observed Levels in DS	Residual Risk and Monitoring Strategy
R-CO-Cl	1.5 ug/day	-	Final aqueous workup	< 10% of TTC	
Intermediate 1	1.5 ug/day	IPC: ≤ TTC prior to workup of Int 2	Consumed by reduction step; little further reduction	30-60% of TTC	
Toluene	890 ppm	≤ 2000 ppm in spec of Int 1	3 drying steps; Purge data	< 10% of PDE	
Palladium	100 ug/day	-	Amount of metal scavenger (redundant GMP control); Purge data; Spiking data	Not detected LOD = 10% of PDE	
Thionyl Chloride	1.5 ug/day	-	4 aqueous workup and drying steps	Scientific principles or data show not present in DS	

Reviewer assessment of impact of excipient properties on CQAs related controls:

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Example: Intra-agency communication

	Definition of Risk			Risk Management during Development	Risk management in Final Control Strategy at Commercial Scale				Residual Risk	
Critical Quality Attribute	Initial Main Risks Identified Prior to Controls	Potential Impact to CQA	Rationale	Process Knowledge	Incoming Materials	CPP or Process Parameter Controls	In-Process Controls	Release Specifications and Methods	Potential Comment to Field	PotentialComments for Post-Marketing
Purity	DS Process Impurity A	H	Potentially Genotoxic, TTC identified	Detailed purging experiments with HIL conditions in API chemistry; no degradation	Starting Material Y specification is limited for impurity precursor.	CPP for reaction tempearture in DS	DS intermediate specification	Final DS Specification, specified monitoring strategy	Verify control or Starting Material Source	Starting Material Y specification is important.
	Form Conversion	M	No difference in solubility.	Confirmation of Form I through DS and DP development and stability; DS process only makes form 1.		CPP in crystallization		Form I confirmation by PXRD		Applicant wants to reduce Form I confirmation in the future.

Critical Quality Attribute	Control Strategy Element	Risk Element/Failure Mode	Communication to Compliance/Investigator
Content Uniformity (Strength)	PAT, Content Uniformity by NIR	Low dose direct compression product/in-homogeneity/segregation	Verify NIR model maintenance strategy.
	Blending Process Operating Ranges	Low dose direct compression product/in-homogeneity during blending	Confirm blending operation and procedures. Confirm sampling strategy.
Purity	Bulk Hold Times	Stability/Degradation by water uptake	Verify bulk hold time studies and justification of hold times.
	Environmental controls	Stability/Degradation by water uptake	Verify low humidity conditions for material handling operations.

Risk assessment can be used as an Intra-agency communication tool.

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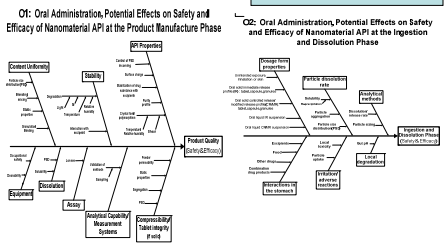
Example: Review teams can assess risk for a *type* of product.

*Excerpts…Ishikawas

Product manufacture → Ingestion and dissolution



*Excerpts…gap analysis

Risk Identified: Risk Factor Category	Sub Risk Factor, Primary and/or Secondary Cause	What do we do or require currently to address this risk? *Guidelines, Policies, Submitted Data, or Research that currently address this risk*	Is this sufficient to address nanomaterial API effects and/or causes? *Identified Area for Improvement*	Potential approach to gap, e.g. proposed solution, references to future or proposed work, if any. *Area of Focus*
Analytical Methods	Dissolution/Release Rate Method	Evaluate dissolution/release rate method development report for discrimination and justification of parameters. Evaluate method against changes in formulation or IVIVR Methods are reviewed following the same requirements for discrimination, development information, etc, regardless of Case A, B, C, or D. For OTC, methods are compendial and evaluation is done against compendial methods. BE data would also catch differences in modified release formulations and could trigger more work on method development information.	For IR, BE studies may need to take into consideration API PSD impact on dissolution for BCS Class II and BCS Class IV. Monographs methods may or may not be suitable for reformulated materials if change to nano API has occurred. Any in-vitro methods that use filtration and are being used for comparative evaluation of quality may need to be evaluated further. The review of any unconventional methodology.	Reminder that for nanomaterials to focus on understanding the effect of particle size distribution on bioavailability and dissolution for Immediate Release, particularly for BCS II and IV, where API PSD may have impact on dissolution Request studies to show API PSD impact on dissolution, a dissolution specification is requested that covers ranges in dissolution may need to show in vivo data ("clinically relevant specs"). Conventional methodology involving filtration of materials in in-vitro analytical methods (e.g. Dissolution, Assay) may need to be revaluated when applied to nano materials.

Ishikawa diagrams and gap analysis of the identified risks are being used to generate risk management plans for the review of nanotechnology products. This approach can help inform development of policy and guidance.

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**OPS/OCP Advisory Committee Meeting August 9, 2012*

Conclusions

- Formal risk assessment in an NDA is not required, but can be very beneficial to the review process.
  - The summary of a risk assessment exercise can be an effective way to communicate the rationale for development and adequacy of a control strategy.
  - Industry can use risk assessment to prioritize development and to focus on high risk areas for quality risk management.
- Reviewers can use risk assessment to confirm adequacy of control strategy and to prioritize the review.
- There is overall flexibility in the use and presentation of risk assessment tools, as long as, risk factor definitions, rationale, and links to supportive data are captured.
- Risk-based communications could facilitate transparency within a quality risk management framework.

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Thank you!

Questions, comments, concerns:

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